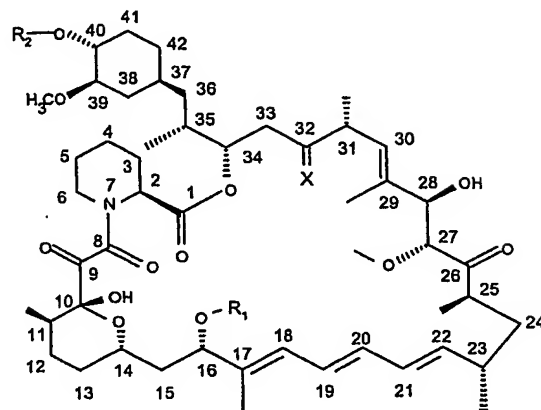


CLAIMS

1. Use of a rapamycin derivative of formula I



wherein

R_1 is CH_3 or C_{3-6} alkynyl,

R_2 is H or $-\text{CH}_2-\text{CH}_2-\text{OH}$, 3-hydroxy-2-(hydroxymethyl)-2-methyl-propanoyl or tetrazolyl,

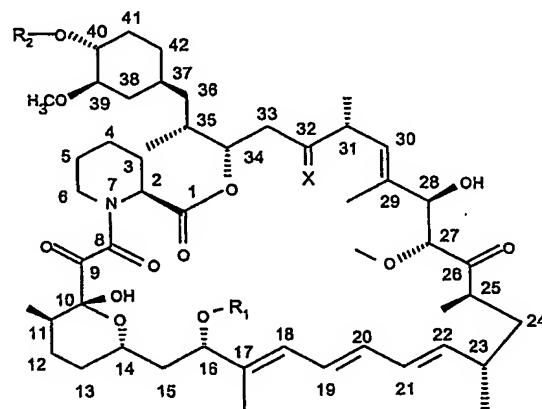
and X is $=\text{O}$, (H,H) or (H,OH),

provided that R_2 is other than H when X is $=\text{O}$ and R_1 is CH_3 ,

or a prodrug thereof when R_2 is $-\text{CH}_2-\text{CH}_2-\text{OH}$, e.g. a physiologically hydrolysable ether thereof

in the preparation of a pharmaceutical composition for the treatment of abnormally increased bone turnover or resorption.

2. A pharmaceutical composition for use in the treatment of abnormally increased bone turnover or resorption comprising a rapamycin derivative of formula I



wherein

R₁ is CH₃ or C₃₋₆alkynyl,

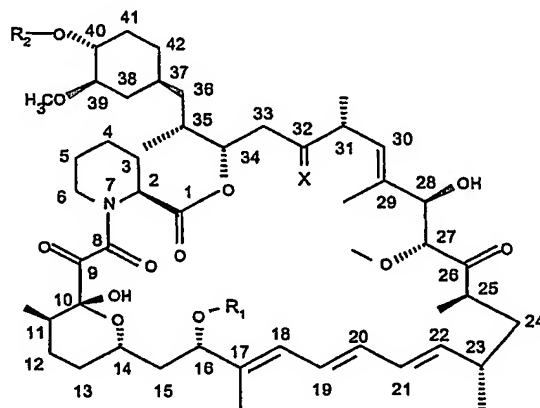
R₂ is H or -CH₂-CH₂-OH, 3-hydroxy-2-(hydroxymethyl)-2-methyl-propanoyl or tetrazolyl, and X is =O, (H,H) or (H,OH),

provided that R₂ is other than H when X is =O and R₁ is CH₃,

or a prodrug thereof when R₂ is -CH₂-CH₂-OH, e.g. a physiologically hydrolysable ether thereof,

together with one or more pharmaceutically acceptable diluents or carriers therefor.

3. A pharmaceutical combination comprising rapamycin or a rapamycin derivative and a second drug selected from bone resorption inhibitor, a calcitonin or an analogue or derivative thereof; a steroid hormone, a partial estrogen agonist or estrogen-gestagen combination; a selective estrogen receptor modulator; vitamin D or an analogue thereof; Parathyroid Hormone (PTH), a PTH fragment or a PTH derivative; a bisphosphonate; a cathepsin K inhibitor; a PTH releaser; a selective androgen receptor molecule; and strontium ranelate.
4. A method for treating abnormally increased bone turnover or resorption in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of a rapamycin derivative of formula I



wherein

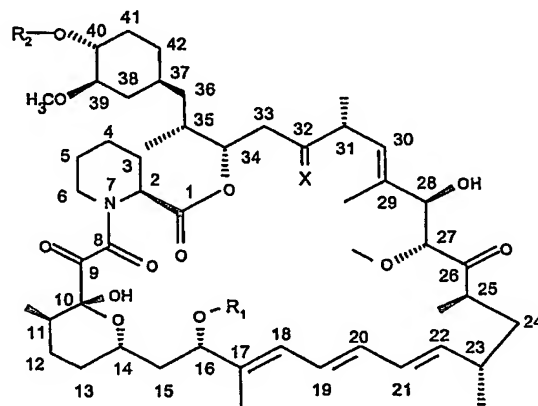
R₁ is CH₃ or C₃₋₆alkynyl,

R₂ is H or -CH₂-CH₂-OH, 3-hydroxy-2-(hydroxymethyl)-2-methyl-propanoyl or tetrazolyl, and X is =O, (H,H) or (H,OH),

provided that R₂ is other than H when X is =O and R₁ is CH₃,

or a prodrug thereof when R_2 is $-\text{CH}_2\text{CH}_2\text{OH}$, e.g. a physiologically hydrolysable ether thereof.

5. A method for treating abnormally increased bone turnover or resorption in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of rapamycin or a rapamycin derivative, concomitantly or sequentially with a second drug selected from bone resorption inhibitor, a calcitonin or an analogue or derivative thereof; a steroid hormone, a partial estrogen agonist or estrogen-gestagen combination; a selective estrogen receptor modulator; vitamin D or an analogue thereof; Parathyroid Hormone (PTH), a PTH fragment or a PTH derivative; a bisphosphonate; a cathepsin K inhibitor; a PTH releaser; a selective androgen receptor molecule; and strontium ranelate.
6. Combination of claim 3 or method according to claim 5 wherein the rapamycin derivative is a compound of formula I



wherein

R_1 is CH_3 or C_{3-6} alkynyl,

R_2 is H or $-\text{CH}_2\text{CH}_2\text{OH}$, 3-hydroxy-2-(hydroxymethyl)-2-methyl-propanoyl or tetrazolyl, and X is $=\text{O}$, (H,H) or (H,OH),

provided that R_2 is other than H when X is $=\text{O}$ and R_1 is CH_3 ,

or a prodrug thereof when R_2 is $-\text{CH}_2\text{CH}_2\text{OH}$, e.g. a physiologically hydrolysable ether thereof.

7. Use, composition, combination or method according to any preceding claim wherein the rapamycin derivative is selected from 40-O-(2-hydroxyethyl)-rapamycin, 40-[3-hydroxy-2-(hydroxymethyl)-2-methylpropanoate]-rapamycin, 40-epi-(tetrazolyl)-rapamycin, 32-deoxorapamycin, 16-pent-2-ynloxy-32(S)-dihydro rapamycin, and TAFE-93.

8. Use, composition, combination or method according to any preceding claim wherein the rapamycin derivative is 40-O-(2-hydroxyethyl)-rapamycin.
9. Use, composition, combination or method according to any preceding claim for the treatment of osteoporosis; bone loss secondary to or due to medication; bone loss associated with immobilisation and space flight; bone loss associated with rheumatoid arthritis, osteopenia, osteogenesis imperfecta, hyperthyroidism, anorexia nervosa, organ transplantation, joint prosthesis loosening; periarticular bone erosions in rheumatoid arthritis; osteoarthritis; hypercalcemia; bone cancer and bone metastases; and/or multiple myeloma.